Understanding Lyophilization Regulations, Being Prepared for FDA Audits & Review Issues

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1

The views expressed during this presentation are my own and may not be those of the FDA.

2

Overview

- Introduction
- Applicable U.S. Regulations & Guidance Documents
- Recent Issues Regarding Lyophilization of Biological Products:
  - Inspection Triggers & FDA 483 Observations
  - Compliance Issues
  - Complete Response Letter Issues
- Summary

3

Introduction - Goals

- Understand general U.S. requirements
- Demonstrate product meets standards
- Prepare for inspections - when, what, how
- Inspection, review and compliance issues
- What can be done to facilitate approvals

4

Applicable U.S. Regulations for Lyophilized Products

- Title 21 CFR Sections 211 “GMPs” & 600, as applicable to product category
- 601.12 *Changes to an Approved Application*
- 600.3(r) Definitions *Purity*
- 610.13(a)(1) Purity *Test for Residual Moisture*

5

Applicable U.S. Regulations for Lyophilized Products

- 211.137 (g) Expiration dating information of reconstituted drugs for investigational use
- 211.166 (a) (5) Stability Testing. Perform stability testing of drug after reconstitution

6

Applicable Guidance Documents

- ***Guide to Inspections of Lyophilization of Parenterals*** (7/93)
  - -Document Focus:
    - -Formulation of products
    - -Aseptic Filling
    - -Cycle, Controls, Validation and Sterilization
    - -Finished Product Testing & Inspection

7

Applicable Guidance Documents

- *Inspection Technical Guide: Lyophilization of Parenterals* (4/8/86). www.fda.gov/ora/inspect_ref/itg/itg43.html
  - – Document Focus:
    - Formulation
    - Filling
    - Sterilization
    - Finished Product Testing

8

Applicable Inspection Documents
FDA Compliance Program Guidance Manual*, 7356.002A, *Sterile Drug Inspections (9/93), Freeze-Drying (Lyophilization) section

If lyophilization is performed by an outside firm, report the firm's name and address.

If lyophilization is performed in-house, report the following:

- Manufacturer of lyophilizer.
- Percentage of firm's products which are lyophilized.
- Describe the heating & cooling systems used in the lyophilizer; the vacuum system; what gas is used to break the vacuum and whether it is sterile; and the temperature controlling system.
- Briefly describe preparation of the sterile product for drying, including procedures for protecting the product from contamination while loading into the lyophilizer.

9

Applicable Inspection Documents
FDA Compliance Program Guidance Manual*, 7356.002A, *Sterile Drug Inspections (9/93), Freeze-Drying (Lyophilization) section *(continued)*

- How is stopper seating of vials performed?
- If performed automatically, is it under vacuum, or if not under vacuum, what gas is used and how is it sterilized?
- Review at least three lyophilization production records for the product referenced above; are the cycle parameters and observed results within the validated cycles?
- What are the firm's criteria for acceptable vs. unacceptable runs, including general appearance, moisture, etc.?

10

Applicable Review Documents

Guidance for Industry: Content & Format of Chemistry, Manufacturing & Controls Information & Establishment Description Information for a Vaccine or Related Product

(1/99)

- Section G. **Lyophilization**:
  - A validation summary for lyophilization of the drug product should be given which includes:
    - A narrative description of the validation (or protocol);
    - Certification that IQ and OQ have been completed;
    - A validation data summary;
    - Explanation of all excursions or failures; and
    - Deviation reports and results of investigations of all excursions or failures.

11

Applicable Review Documents

Guidance for Industry: For the Submission of Chemistry, Manufacturing … for Human Plasma-Derived Biological Products, Animal or Serum-Derived Products

(2/99)

- Part 2- Establishment Description Section; III. **Specific Systems**; Section D. **Lyophilization**:
  - Validation summary for lyophilization of the drug substance/product should be given, which includes:
    - A narrative description of the validation (or protocol);
    - Certification that IQ and OQ have been completed;
    - A validation data summary;
    - Explanation of all excursions or failures; and
    - Deviation reports and results of investigations of all excursions or failures.

12

Applicable Review Documents

Guidance for Industry: Content & Format of Chemistry, Manufacturing … for a Biological In vitro Diagnostic Product (3/99)

- II. In Vitro Product; Section (c) *Methods of Manufacturing & Packaging*:
  - A complete description of the manufacturing process flow for each formulated bulk should be provided. This discussion **should include a description of** … vialing/filling, **lyophilization**, labeling, and packaging procedures.

13

Applicable Review Documents

Guidance for Industry: Content & Format of Chemistry, Manufacturing … for a Biological In vitro Diagnostic Product (3/99)

- II. In vitro Product; Section G. *Stability*:
  - Stability data supporting the proposed shelf-life of the reconstituted in vitro product for all labeled dilutions should be provided.

14

Inspection Triggers

- Inadequate understanding of product characteristics (thermal properties of formulation)
- Inconsistent manufacture of product
- Inadequate understanding of the process & equipment
- Inadequate validations performed, not documented, or not available

15

Inspection Triggers

- Legacy systems & products
- Non-sterilizable lyophilizers
- Minimal (or non-existent) routine maintenance on lyophilizer and support components
- Different lyophilizer models with identical cycle for different fill volumes or products – “one cycle fits all”
- Excessively long lyophilization cycles

16

Inspection Triggers

- Cycles controlled by only one TC
- Use of non-validated containers (no validation of stability data available to support alternate containers)
- Maximum allowable reconstitution limits not based on historical data
- Final product sampling locations not specified, or no rationale for choice of location
- Small sample sizes tested (particularly during validation)

17

Inspection Triggers

- Variability in C/C integrity testing results
- Evidence of broken or damaged vials during lyophilization
- Unseated or popping stoppers
- Stoppers sticking to shelf bottoms
- Inadequately defined & quantified physical characteristics, appearance of final product

18

Recent FDA Observations Regarding Lyophilization

19

Process Validation

- There are no data available for moisture mapping studies performed on actual full-scale production runs.
- Process validation study samples were not collected for shelves 8 through 10, shelves 8 and 9 have been used during production.

20

Process Validation

- There are no data available to support the acceptability of the lyophilization cycle that was transferred directly from the previous lyophilizer to the new lyophilizer.
- "Margin testing" of allowable ramp rate ranges were not evaluated during PQ studies performed.

21

Bulk Tray Lyophilization

- Representative sampling of the lyophilized bulk product cake may not always be performed in that the cake is stratified. Sampling procedures do not specify to collect differing morphological levels of the final cake.
- New stainless steel trays of different dimensions have not been qualified for use in bulk tray lyophilization. In addition, the location of TC placement in the trays are not specified.

22

Recent FDA 483 Observations - Qualification

- There are no data available to support the suitability and acceptability of the surrogate formulation used during lyophilization cycle validation which included 90 vials containing product and 10,000 surrogate vials containing NaCl, glycine and 5% protein.

23

Validation of the Lyophilization Cycle

- Studies have not been performed to evaluate the physico-chemical properties of the formulation (i.e., freezing and collapse temperature).
- There are no data available to support the acceptability of reprocessing operations that are specified in the batch record stating that the primary and secondary drying cycles can be run again, allowing for the storage of partially lyophilized product.

24

Recent FDA 483 Observations - Aseptic Processing

- Media fill procedures do not include a challenge of the entire process in that there are no provisions for fill set-up, fill volume adjustments, removal of mis-stoppered vials, personnel interventions/interruptions, and cumulative tray loading activities.

25

Recent FDA 483 Observations - Aseptic Processing

- No instructions available for transporting vials from the filling room to the lyophilizer.
- Environmental monitoring is not conducted in the Class 100 lyophilizer loading areas.

26

Recent FDA 483 Observations - Aseptic Processing

- Air quality in the lyophilizer loading area is Class 100,000.
- Lyophilizer door extends outside the Class 100 area during chamber loading operations.

27

Recent FDA 483 Observations - Aseptic Processing

- Nitrogen is used to backfill lyophilizer chamber during media fill studies.
- Portions of the media fill are frozen in the lyophilizers in order to simulate the actual cycle.

28

Recent FDA 483 Observations - Aseptic Processing

- Loading boxes used to transport filled vials through unclassified areas to lyophilizers are not all included in the microbial monitoring program.
- There are no sterilizing grade vent filters on the lyophilizer chamber.
- Integrity testing of the sterilizing grade vent filter for the condenser has not been performed.

29

Recent FDA 483 Observations - Aseptic Processing / Qualification

- There are no data available to support the acceptability of the six day hold time during the freezing stage in the lyophilizer.
- No specified maximum allowable hold time for filled, partially stoppered, vials prior to loading and freezing in lyophilizer.
- Lyophilization cycle was discontinued due to equipment malfunction. Trays of product involved were lyophilized again one week later. Investigation did not evaluate possible effect/s on product stability.

30

Recent FDA 483 Observations - Qualification

- Batches are not uniformly frozen in that lyophilizer shelves are pre-frozen to –40° C prior to loading, which can take up to two hours to complete.

31

Recent FDA 483 Observations - Qualification

- No data available from any lyophilization run to correlate product temperature to shelf temperature, in any lyophilizer used.
- Thermocouples used to monitor temperatures during lyophilization cycles are not calibrated.

32

Recent FDA 483 Observations - Qualification

- Four thermocouples were used in each qualification run. Only four shelves out of ten were ever monitored during the qualification to demonstrate shelf temperature uniformity.

33

Recent FDA 483 Observations - Qualification

- Thermal mapping representative of each shelf has not been performed.
- Shelf temperature mapping studies performed did not include the primary drying temperature of –50 °C.

34

Recent FDA 483 Observations - Qualification

- Lyophilizers are not routinely re-qualified.
- Lyophilizer incapable of meeting predetermined criteria for leak rate in current condition due to excessive leak rates exceeding the maximum allowable level.

35

Recent FDA 483 Observations - Qualification

- Maximum load configuration employed during validation does not reflect maximum capacity of the equipment. In addition, there are no specifications in the batch records limiting use to only the load configurations that had been validated.

36

Recent FDA 483 Observations - Qualification

- Lyophilizer cycle changes made for __ml vials had not been validated. Cycle changes were implemented for the vacuum set points and secondary drying time to correct melt back and foaming problems.
- Cycle times are defined as not less than X hours. Maximum allowable time limits for the cycle times were not specified, nor were they established during validation studies.

37

Recent FDA 483 Observations - Qualification

- Insufficient data to support the process qualification in that two vials/shelf were tested for residual moisture, one vial/shelf was tested for potency and three vials/lot tested for pH, reconstitution and osmolarity. Sampling locations within the unit were not defined, with lot sizes ranging from 7600 to 10,000 vials.

38

Recent FDA 483 Observations - Qualification

- Three vials were tested for residual moisture and six for potency for each qualification lot produced. The locations of the test samples were not defined and lot sizes ranged from 5000 to 12,000 vials.

39

Recent FDA 483 Observations - Qualification

- Residual moisture samples were collected from two opposite corners of seven of the ten shelves used during production.

40

Recent FDA 483 Observations - Qualification

- Retrospective validation data was used to qualify the lyophilization process. Testing data did not demonstrate uniformity or reproducibility of the process.

41

Recent FDA 483 Observations - Sterilization

- Lyophilizers are not sterilizable and are not sanitized.
- Sterilization of the baffle was not evaluated during sterilization validation studies.
- Lyophilizer steam sterilization cycles are not revalidated annually.

42

Recent FDA 483 Observations - Sanitization

- Lyophilizer is not steam sterilizable and phenolic sanitizers are used for lyophilizer chamber sanitization. Removal of phenolic residues from chamber has not been qualified. Final product impurity profile testing revealed presence of phenol in the final product.

43

Recent FDA 483 Observations - Cleaning

- Lyophilizer is not cleaned prior to product changeover.
- Cleaning & sanitization procedures have not been qualified.
- Cleaning validation studies did not incorporate surface sampling and testing. Interior surfaces are visually inspected for cleanliness.

44

Recent FDA 483 Observations - Cleaning

- Chamber and surfaces are not periodically monitored for the presence of residual oil or thermal transfer fluid.
- Periodic monitoring for the presence of thermal transfer fluids in the lyophilizer chamber is not performed post-use.

45

Recent FDA 483 Observations - Finished Product Testing

- Routine moisture testing is not performed on lyophilized products.
- There are no data available to support the acceptability of the residual moisture specification established for final lyophilized product.

46

Recent FDA 483 Observations - Finished Product Testing

- Stability program for lyophilized product does not include moisture testing.
- Stability studies did not include testing to support the acceptability of label claims for use within specified times following reconstitution. The last study verifying label claim for use after reconstitution was performed four years ago.

47

Recent FDA 483 Observations - Finished Product Testing

- SOP for moisture determination allows averaging out of specification values into specification.

48

Recent FDA 483 Observations - Finished Product Testing

- Not all fill volumes had been included in the qualification studies or testing performed to support the acceptability of the lyophilization cycle.

49

Recent FDA 483 Observations - Finished Product Testing

- No specification has been established for maximum acceptable reconstitution times which vary from instantaneous to seven minutes.
- Specified reconstitution times greatly exceeded historical times noted during stability testing.

50

Recent FDA 483 Observations - Change Control

- Changes are implemented without QA approval. For example, in-process moisture specification was changed from 1-3% to 1.5-3.5% without a complete product evaluation being performed.

51

Summary Points

- Incorporate and document all possible (realistic) interventions in your media fill operations.
- Lyophilizer loading should be performed in areas that are demonstrated to be of similar environmental classifications as the aseptic filling.

52

Summary Points

- Media fills should include transport of vials to lyophilizer and mimic actual loading conditions as much as possible.
- Perform dynamic smoke studies in lyophilizer loading areas.
- Do not create conditions inhospitable to growth during media fills (replace inert gas with sterile filtered compressed air during media fills).

53

Summary Points

- Do not introduce uncleaned or non-sterilized vials into a lyophilizer load.
- Include transport boxes and tray rings in the routine microbial monitoring program.
- Perform microbial monitoring on all personnel performing loading operations.

54

Summary Points

- Trust but verify. Make sure that your operators are well trained and perform frequent audits of aseptic processing areas.
- Retrain operators as required and document training performed.

55

Summary Points

- Establish and validate maximum/minimum allowable times for each phase of the process. Specify and document these times in your procedures or batch records.
- Evaluate possible effects on stability and product when unforeseen manufacturing events occur.

56

Summary Points

- Document all the hard work done during validation and qualification activities.
- Calibrate all instrumentation used during validations.

57

Summary Points

- Product and shelf temperatures differ. Have data demonstrating that you know exactly what these temperature differences could be.
- Assure that uniform freezing conditions are provided to all vials.
- Map all shelves in your system to demonstrate temperature uniformity.

58

Summary Points

- Determine appropriate requalification timeframes for lyophilizers.
- Institute and document the preventative maintenance program for lyophilizers so that they can continue to meet performance criteria.

59

Summary Points

- Validate any cycle changes implemented.
- Have sufficient final product testing data available to support validations. Document locations of samples tested. Do not rely exclusively on release criteria.
- Demonstrate uniformity and reproducibility of lyophilization process through sufficient final product testing.

60

Summary Points

- Use appropriate sample sizes when testing final product characteristics.
- Sterilize the lyophilizer, condenser, and support piping.

61

Summary Points

- If multi-product unit, validate cleaning procedures to assure removal of residual product.
- Monitor chamber for residual oils and heat transfer fluids using qualified methods.

62

Summary Points

- Perform integrity testing of nitrogen or compressed air filters and vent filters.
- Perform routine moisture testing of your product and have data to support potency and stability of both the upper and lower moisture specifications.

63

Summary Points

- Include stability testing that supports all claims made in the labeling, such as specified times for use after reconstitution.
- Evaluate your product thoroughly if changes in the final product characteristics are noted.

64

Summary Points

- Do not average out of specification results.
- Include all fill volumes and vial sizes in validation studies.
- Reconstitution times should reflect historical data and should be consistent.
- Evaluate possible impact of revised specifications to product quality and stability prior to changing specifications for approved products.

65

Conclusions

- **Contact** the Agency to discuss process or specification changes prior to implementation.
- **Request a meeting** to discuss your proposed changes.
- Manufacture adequate **back-up inventory** prior to initiation of major changes to approved equipment or processes.
- **Notify** the appropriate Division as to when your supplement will arrive.

66